UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/003,468	10/23/2001	Fatemeh Mojtabai	FMI-001	4328

959 7590 03/30/2005

LAHIVE & COCKFIELD, LLP.
28 STATE STREET
BOSTON, MA 02109

EXAMINER
LEE, MATTHEW C

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 03/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/003,468	MOJTABAI, FATEMEH	
	Examiner	Art Unit	
	Matthew C. Lee	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,55-58 and 63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,55-58 and 63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 May 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Amendments

Applicant's amendment to claims filed on October 3, 2005 has been entered.

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-8 and 55-58, is acknowledged. Applicant further elected "membrane protein" as the species of proteins to be examined in claims 4 and 57; "gas-aqueous interface" as the species of interface in claims 1-8 and 55-58; and "proteoliposomes" as the species of materials used to apply the proteins to the interface in claim 6. The election of species was also made without traverse.

The newly added claim 63 is grouped with Group I as it is drawn to the same invention.

Currently, claims 1-8, 55-58 and 63 are pending.

Claim Rejections – 35 U.S.C. 112 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-6, 8, 55-58 and 63 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 2D and 3D geometrically ordered structures, does not reasonably provide enablement for the formation of any arbitrarily

chosen ordered structures. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. The factors to be considered in determining what constitutes undue experimentation were affirmed by the court in *In re Wands* (8 USPQ2d 1400 (CAFC 1986)). These factors are (1) the quantity of experimentation; (2) the amount of direction or guidance presented in the specification; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the art; (6) the level of skill of those in the art; (7) predictability or unpredictability of the art; (8) and the breadth of the claims. See MPEP §§ 2164- 2164.08(c).

The second method step recited in claim 1 states "...compressing said population to an appropriate pressure, such that an ordered structure of said amphiphilic molecules is formed..." The scope of the claim is very broad as the term "ordered" without any further qualification is interpreted to encompass all imaginable types of order with a discernible pattern and the term amphiphilic molecules is interpreted to encompass any amphiphilic molecules. It is acknowledged that the skill in the art is high. However, the nature of the invention relates to organizing and manipulating materials at the molecular level, which is still a very young discipline with a great degree of unpredictability (as also indicated in Example 1 of the specification where the formation of 3D crystal is acknowledged to be an unexpected result). While

the specification has provided examples of ordering COX proteins into crystals, lattice crystal is not the only possible type of ordered structure. Larger molecular assemblages such as ion channels made up of amphiphilic molecules are also considered "ordered" structures, but neither the specification nor the claim has provided sufficient instructions on how to compress a population of amphiphilic molecules into an ion channel. The art is also silent about how to accomplish such complex order through lateral compression of component molecules. It would therefore require one of ordinary skill in the art an undue amount of experimentation to determine the experimental conditions required for forming an arbitrarily chosen ordered structure of amphiphilic molecules by the claimed method. In light of the specification, the method as claimed is only enabled for ordering of amphiphilic molecules into simple 2D or 3D lattice type of structures.

Claims 3-6, 8, 55-58 and 63 are also rejected under 35 U.S.C. 112 1st paragraph for the same reason as set forth above. Claims 3-6 and 8 depend from claim 1 but the further limitation of claim 1 recited in claims 3-6 and 8 do not remedy the deficiency of claim 1; the claims as recited all encompass structures with complex orders. Claims 55-58 and 63 are similarly rejected because they also read on all possible ordered structures of a protein.

Claim Rejections – 35 U.S.C. 112 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In this instant case, Claim 6 recites the limitation "said proteins" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections – 35 U.S.C. 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-8, 55-58 and 63 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility. The claims are all directed to a method of forming ordered structures of an arbitrary amphiphilic molecules, a protein or a membrane protein by applying the molecule of interest to an air-aqueous interface and compressing the molecules. However, without knowing the identify of the molecule of interest or the specific order to be formed, even if the order is simple 2D/3D structure, it is not clear what the structure is to be used for. Such an ordered structure apparently is a starting point for further research (e.g. a crystal structure of an arbitrary protein) at best. Without a specific and substantial utility, the method as claimed lacks patentable utility.

Claim Rejections 35 U.S.C. 102(b)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Verclas et al. (J. Mol. Biol. (1999) 287, 837-843).

Regarding Claim 1, the claim is directed to a method for forming an ordered structure of amphiphilic molecules comprising the steps of applying the amphiphilic molecules to an air/water interface and laterally compressing the molecules to form the desired ordered structure.

Verclas et al. teach a method for making a single layer of purple membrane ordered into 2D crystal array at the air/water interface by forming a Langmuir film wherein lateral pressure is applied to the membrane. The method of Verclas et al. anticipates the method of Claim 1 as follows:

The method of Verclas et al. is a surface method that employs the Langmuir film technique, a well-know technique in surface science (see KSV Instruments USA, http://www.ksvinc.com/LB.htm, for a general background discussion regarding Langmuir film technique). The method deposits membrane extracted from *H. salinarum* (page 838, right col. first sentence of second paragraph) to an air/water interface where the lateral pressure was increased through varying surface tension by way of changing water salinity (page 839, left col. line 3-11). Patches of the membrane were further characterized at various lateral pressures (page 839, left col. line 11-16). Verclas et al.

noted that 2D crystalline structures of the purple membrane were generally found in the film on the water surface in random orientations (page 839, left col. last paragraph).

Here, purple membrane refers to patches of lipid membrane from *H. salinarum* that contain the membrane protein bacteriorhodopsin (see "Growth and Isolation of Purple Membrane", abstract, URL= http://qsad.bu.edu/curriculum/labs/purplemembrane.html). Both membrane and membrane proteins are made up of amphiphilic molecules (see "Lecture 7: Membrane Structure & Functions", page 1, http://members.aol.com/BearFlag45/Biology1A/LectureNotes/lec07.html, and page 3). Thus, the method of Claim 1 is anticipated by the method of Verclas et al. wherein the purple membrane in the method of Verclas et al. corresponds to amphiphilic molecules in the Claim 1, 2D crystalline structure of the purple membrane formed by the method of Verclas et al. corresponds to the desired ordered structure, and various lateral pressure applied through varying surface tension laterally in the method of Verclas et al. corresponds to compressing the molecules in Claim 1.

Claim 2 further limits the pressure applied in Claim 1 to be appropriate to form a 2D ordered structure.

The method of Verclas et al. monitors the structure of the purple membrane by characterizing patches of the membrane at various laterally pressure (page 839, left col. line 3-11). Therefore a pressure appropriate for forming 2D ordered structure is inherently taught by Verclas et al. since 2D crystalline structures were observed in the method of Verclas et al.

Claim 3 further limits the amphiphilic molecule of claim 1 to be a protein. Claim 4 further limits the protein of claim 3 to be a membrane protein.

The method of Verclas et al. uses purple membrane, which comprises the membrane protein bacteriorhodopsin (page 838, right col. 2nd paragraph), therefore, claims 3 and 4 are also anticipated by Verclas et al.

Claim 5 is interpreted here to mean that the lipids and the amphiphilic molecules of claim 1 are present together at the interface. Claim 6 further limits the interface of claim 1 to be in proteoliposomes, liposomes or a cellular membrane. Claim 8 further limits the interface of claim 1 to be a gas-aqueous interface.

The further limitations recited in claims 5, 6 and 8 are all anticipated by the method of Verclas et al. as follows:

Regarding Claim 5 and 8, Figure 1 on page 838 clearly shows that the purple membrane is located at the water/air interface. Since purple membrane contains both the membrane protein bacteriorhodopsin and lipids (see "Growth and Isolation of Purple Membrane", abstract), Claim 5 and 8 are also anticipated by the method of Verclas et al.

Claim 6 is also anticipated by the method of Verclas et al because the membrane used in the method of Verclas et al. is a cellular membrane from *H. salinarlum* (page 838, left col. 2nd paragraph).

Claim Rejection – 35 U.S.C. 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Verclas et al. as applied to claims 1-6 and 8 set forth above in the 102(b) rejection, in view of Hemming et al. (JMB (1995) 246. 308-316) and in further view of Koppenol et al. (J. of Pharmaceutical Sci. Vol 86, No 11, 1997).

Claim 7 is directed to the method of claim 1 within the further limitation that the applied pressure forms a 3D ordered structure.

Verclas et al. teach the method of claim 1. Verclas et al. also teach that it is possible to fuse single individual smaller crystals to form large single crystals (page 841, right col. Conclusion, 1st paragraph, lines 7-13).

Verclas et al. do not teach actually apply appropriate pressure to form 3D ordered structure.

Hemming et al. teach that 2D crystals of proteins on lipid monolayer can initiate the formation of large 3D crystals through epitaxial growth under suitable conditions where a 2D crystal serves as the seed for further growth into 3D crystal (Hemming, abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to try to fuse small 2D crystal structures into a larger crystal as taught by Verclas et al. and to find appropriate pressure at which 3D crystal forms through

epitaxial crystal formation as taught by Hemming et al. where the motivation would have been to use the 2D crystal as a catalyst for the 3D crystal growth of difficult to crystallize proteins as taught by Koppenol et al. (Koppenol et al. page 1207, left col. lines 15-21).

Claims 55-57 are rejected under 35 U.S.C. 103(a) as unpatentable over Verclas et al. as applied to claims 1-6, and 8 set forth above in the 102(b) rejection, in view of Hohenfeld et al. (FEBS Letters 442 (1999) 198-202) and in further view of Koppenol et al. (J. of Pharmaceutical Sciences. Vol 86 No 11 (1997) 1204-1209).

Claim 55 is directed to a method for fabricating an ordered structure of a protein comprising the steps of expressing the protein in a cell, obtaining the protein from the cell, apply the protein to an interface, and then compressing the protein at the interface to form an ordered structure. Claim 56 is interpreted to be expression of a protein in a cell expression system with modified expression regulation to express the protein in quantities in excess of its natively expressed amount. Claim 57 further limits the protein to be a membrane protein. Claim 58 is interpreted to be that the membrane protein and the membrane lipids are present together at the interface.

Verclas et al. teach a method for forming an ordered structure of a protein by applying the protein embedded in a lipid membrane to an air/water interface and compressing the protein into an ordered structure, as set forth in the 102(b) rejection of claims 1-6 and 8.

Verclas et al. do not teach producing the protein in cell expression system or overexpressing the protein.

Hohenfeld et al. teach a method of overexpressing bacteriorhodopsin in *E. coli* (Hohenfeld, abstract and pages 198-199, sections 2.3 and 2.4).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the membrane overexpression strategy as taught by Hohenfeld et al. in the method of Verclas et al. instead of extracting proteins directly from wild-type bacteria, where the motivation would have been to generate larger quantities of membrane protein to promote higher protein concentration at the interface which is a requirement for 2D crystal formation (Koppenol et al. page 1204, right col. 1st paragraph, lines 4-5).

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Matthew C Lee whose telephone number is (571) 272-2931. The examiner can normally be reached on 9am - 5pm, Mon - Fri..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Matthew C Lee, Ph.D.
Examiner
Art Unit 1631

March 18, 2005

Ardin H. Marschel 3/23/05
ARDIN H. MARSCHEL
PRIMARY EXAMINER